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Evaluation of Systemic *Candida* Infections in Pediatric Burn Patients

Pediyatrik Yanık Hastalarında Sistemik *Candida* Enfeksiyonlarının Değerlendirilmesi

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Abstract

Objective: *Candida* infection is one of the important causes of morbidity and mortality in burn injuries. In our study, it was aimed to evaluate pediatric patients hospitalized for burns and found to have bloodstream infections due to *Candida* species.

Material and Methods: In our study, patients who were followed up in the burn service of a tertiary childcare hospital between June 2007 and December 2022 and who had *Candida* growth in their blood culture were evaluated.

Results: There were 38 patients with *Candida* growth in blood culture. Median age of the patients with growth was 23.5 (8-163 months) months and the median reproductive day was the 13th day of hospitalization. While *Candida albicans* was detected in 21 (55.3%) of the patients, non-albicans *Candida* was detected in 17 (44.7%) patients. There was no difference between the two groups in terms of clinical and laboratory findings.

Conclusion: As a result, fungal infection should be kept in mind in pediatric burn patients in the growth in the 2nd week.

Keywords: Burn, *Candida*, children

Öz

Giriş: *Candida* enfeksiyonu yanık yaralanmalarında görülebilen önemli morbidite ve mortalite nedenlerinden biridir. Çalışmamızda yanık nedeniyle yatırılan ve *Candida* türlerine bağlı kan dolaşımı enfeksiyonu saptanan pediyatrik hastaları değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamızda, Haziran 2007-Aralık 2022 tarihleri arasında üçüncü basamak çocuk hastanesi yanık servisinde izlenen ve kan kültüründe *Candida* üremesi olan hastalar değerlendirildi.

Bulgular: Kan kültüründe *Candida* üremesi olan 38 hasta saptandı. Üreme saptanan hastaların ortanca yaşı 23.5 (8-163 ay) ay ve ortanca üreme günü yatışının 13. günüydü. Hastaların 21 (%55.3)'inde *Candida albicans* saptanırken, 17 (%44.7)'sinde ise non-*albicans Candida* saptandı. Her iki grup arasında klinik ve laboratuvar bulguları açısından fark saptanmadı.

Sonuç: Sonuç olarak pediyatrik yanık hastalarında ikinci hafta içinde olan üremelerde mantar enfeksiyonu akılda tutulmalıdır.

Anahtar Kelimeler: Yanık, *Candida*, çocuk

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Introduction

Burn injuries are a global public health problem causing approximately 180.000 deaths annually, mostly in low- and middle-income countries. It is reported that 80-90% of burns occur in homes and are usually caused by hot liquids, flames, or stove explosions in the kitchen (1). When age groups are taken into consideration, it has been shown that burn injuries occur more frequently especially in the childhood and the risk of morbidity is higher in pediatric patients compared to adult patients (1-3).

Burn patients are more susceptible to infections due to loss of the natural skin barrier and immunosuppression, and secondary infections significantly increase mortality and morbidity (4). Despite advances in medical care, 75% of all deaths in patients with severe burns are associated with sepsis due to microorganisms or complications of burn wounds (5). Although bacteria are the most common cause of burn infections, the incidence of fungal infections has also increased with the increased use of broad-spectrum antimicrobials (6).

In our study, it was aimed to evaluate the demographic characteristics, risk factors and *Candida* species detected in pediatric patients hospitalized for burns.

Materials and Methods

This single-center study was conducted in a tertiary care children's hospital, which is the pediatric referral center for burn patients in Türkiye. Among the pediatric patients between the ages of one month and 18 years who were hospitalized in the burn ward of our hospital between June 2007 and December 2022, those with *Candida* growth in catheter and peripheral blood cultures were included in our study. Patient data were screened through patient information system records and patient files. Demographic characteristics of the patients such as age, sex, and total body surface area were determined by retrospective scanning. Data such as species, antifungal susceptibility, day of growth, clinical and laboratory markers at the time of growth, antibiotics used before bloodstream infection due to *Candida* were analyzed. During the period of *Candida* growth in culture, the presence of fever, complete blood count (white blood cells, hemoglobin, platelet counts) and C-reactive protein (CRP) levels were evaluated. In addition, patients with *Candida albicans* and non-*albicans Candida* growth were compared, and risk factors were evaluated.

Ethics committee approval was obtained by the local ethics committee with protocol number 817 dated 23.02.2023.

Statistical analyses were performed with SPSS Statistics 17.0 (International Business Machines Corp, Armonk, NY) package program. Categorical variables were presented as frequency and percentages, and numerical variables were presented as (mean ± standard deviation) or (median) range (maximum, minimum) using tables. Chi-square analysis method was preferred to determine the relationship between categorical variables. A value of $p< 0.05$ was considered statistically significant in the entire study.

Results

Candida growth was detected in the blood cultures of 38 (0.76%) of 4976 pediatric patients hospitalized in the burn unit in a fifteen-year period. Of the growths, 28 (73.7%) were found in peripheral blood cultures and 10 (26.3%) in catheter blood cultures. Median age of the patients was 23.5 months (8-163 months). Twenty-three (60.5%) of the patients were males and 15 (39.5%) were females. Thirty (78.9%) of the patients' burns were hot liquid burns and eight (21.1%) were flame burns. The mean burn area was 33.7 ± 18.3% (min-max= 5-90%), 29 (76.3%) patients had a burn area below 50% and 9 (23.7%) patients had a burn area above 50%. *Candida* growth in blood cultures was detected on the median 13th day of hospitalization (min-max= 2-65 days). In 10 patients with catheters, growth was detected on a median of 16 ± 9.6 (min-max= 3-37) days after catheter insertion. Ten (26.3%) of the patients received supportive treatment with total parenteral nutrition (TPN). All patients were receiving antibiotic treatment at the time of culture or had received systemic antibiotic treatment before. Median duration of antibiotic treatment was seven days (min-max= 1-38 days), 16 patients received glycopeptides, 15 patients received beta-lactam/beta-lactamase inhibitors and 10 patients received carbapenem treatment. Three patients (7.9%) had simultaneous *Candida* growth in burn site culture (Table 1).

Table 1. Evaluation of risk factors in patients with *Candida* growth in blood culture

Risk factors		**n**
Age		23.5 month (8-163 months)
Sex	Male	23 (60.5%)
	Female	15 (39.5%)
Burn percentage		33.7 ± 18.3%
TPN use		10 (26.3%)
Catheter use		10 (%26,3)
The insertion day of catheter		16 ± 9.6 days
Antibiotic use		38 (100%)
Antibiotic duration		Seven day (min-max= 1-38 days)
Antibiotic received	Glycopeptide	16
	Beta-lactam/ Beta-lactamase inhibitor	15
	Carbapenem	10

When the growths were evaluated according to *Candida* species, *Candida albicans* was the most common species (21/38 patients 55.3%). When non-*albicans Candida* growths were evaluated, *C. tropicalis* was detected in seven (18.4%) patients, *C. parapsilosis* in six (15.8%) patients, *C. glabrata* in two (5.3%) patients, *C. crusei* in one (2.6%) patient and *C. kefyr* in one (2.6%) patient out of 17 (44.7%) patients (Table 2).

When we divided the *Candida* growths into two groups as *albicans* and non-*albicans* and compared them, 11 (52.3%) of the 21 patients with *Candida albicans* growth were males and 10 (47.7%) were females; 12 (70.5%) of the patients with non-*albicans Candida* growth were males and five (29.5%) were females, and there was no statistically significant difference. Median age of the patients with *C. albicans* growth was 21 months (8-163 months), median age of patients with non-*albicans Candida* growth was 24 months (8-115 months), and there was no statistically significant difference between the two groups (p> 0.05). Of the catheter culture growths, four (40%) were *C. albicans*, three (30%) were *C. parapsilosis*, one (10%) was *C. tropicalis*, one (10%) was *C. glabrata*, and one (10%) was *C. cruzei*.

In patients with *Candida albicans* growth, serum white blood cell count was 12914 (± 1865) $x10^9$/L, hemoglobin level was 10.1 (± 2.1) g/dL, platelet count 429800 (± 105307) $x10^9$/L , neutrophil count 7433 ± (5648) $x10^9$/L, CRP level 9.5 (± 1.4) mg/dL. In patients with non-*albicans Candida* isolation, mean white blood cell count was 10303 (± 1599) $x10^9$/L and hemoglobin count was 9.8 (± 1.3) mg/dL, platelet count was 355153 (± 199271) $x10^9$/L, neutrophil count was 5668 (± 4427) $x10^9$/L, CRP was 9.6 (± 2.5) mg/dL and there was no statistical difference (p> 0.05). Only one of the patients with *Candida albicans* growth had neutropenia (Table 3).

Candida albicans growth was detected on median day 13 (days 2-55) of hospitalization and non-*albicans Candida* growth was detected on median day 13 (days 2-43), and no statistically significant difference was found. When the growths were evaluated by Kaplan-Meier analysis according to the day of hospitalization, 19% of *C. albicans* growths were detected in the first seven days, 33.4% between the 8th and 14th days, 19% between the 15th and 21st days, 23.8% between the 22nd and 40th days, and 4.8% between the 41st and 55th days, while for non-*albicans Candida* growths, these rates were 23.5%, 29.5%, 23.5%, 23.5%, 19.6% and 5.9%, respectively (p> 0.05) (Figure 1) (Table 4). The susceptibility results of seven patients were evaluated when an antifungal kit was available for antifungal susceptibility studies in our hospital. Two of them were tested for *Candida albicans* and were found to be fluconazole resistant to echinocandin and amphotericin B. Five of them could be studied for non-*albicans Candida* growths. Three of these were *Candida tropicalis* growths, two of which were susceptible to all antifungals, one was resistant to azole and amphotericin B. Amphotericin B and azole resistance was detected in the blood culture of *Candida cruzei. Candida parapsilosis* was grown in the blood culture of one patient and was found to be azole resistant. In our study, there was no 30-day mortality due to bloodstream infections caused by *Candida* species.

Table 2. Numerical distribution of *Candida* species grown in blood cultures

***Candida* species**	**Number (n)**	**Percentage (%)**
Candida albicans	21	55.3
Candida tropicalis	7	18.4
Candida parapsilosis	6	15.8
Candida glabrata	2	5.3
Candida crusei	1	2.6
Candida kefyr	1	2.6

Table 3. Comparison of *Candida albicans* and non-albicans with growth

	Candida albicans	**Non-*albicans Candida***
Number (n)	21	17
Age, month (min-max)	21 (8-163)	24 (8-163)
Sex, n (F/M)	11/10	12/5
Day of admission (median) day (min-max)	13 (2-55)	13 (2-43)
Serum white blood cell count (mean) $x10^9$/L	12914 (± 1865) $x10^9$/L	10303 (± 1599) $x10^9$/L
Serum hemoglobin level (mean) (g/dL)	10.1 (± 2.1)	9.8 (± 1.3)
Serum platelet count (mean) $x10^9$/L	429800 (± 105307)	355153 (± 199271)
Serum C-reactive protein (mg/dL)	9.5 (± 1.4)	9.6 (± 2.5)

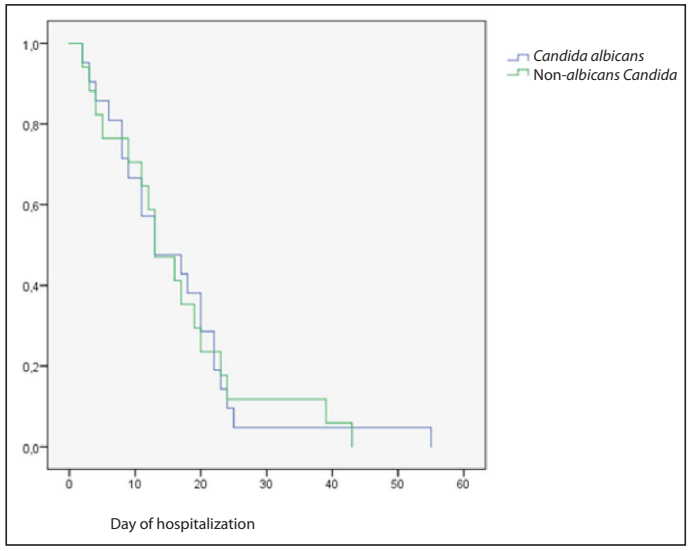

Figure 1. Evaluation of growth according to Kaplan-Meier analysis according to the day of hospitalization: The graph of patients with *Candida albicans* growth in blood culture is indicated with a blue line, and the graph of patients with non-*albicans Candida* growth is indicated with a green line.

Discussion

In our study, 38 patients who were hospitalized in the burn unit during a 15-year period and had *Candida* growth in blood cultures were evaluated, and 55.3% of these patients were *C. albicans*. Median time of growth was the 13th day of hospitalization, antifungal treatment was positively responded and no mortality was observed.

The true incidence and significance of fungal infections in burns is difficult to determine due to problems in detection. Urinary, respiratory tract and skin contamination by fungal agents, especially *Candida* species, is also quite common. It is also very difficult to differentiate between bacterial and fungal infections by clinical symptoms (5). The rate of burns is higher especially in children compared to adults and the most common age group is boys aged 1-5 years (7,8). The median age of our patients was found to be approximately two years and 60.5% were male.

Main risk factors identified for the development of fungal infection in pediatric burn patients include depth of injury, presence of inhalation injury, presence of permanent devices, extensive burns covering more than 50% of the total body surface area, immunosuppression, neutropenia, long-term use of antibacterial therapy, use of vasoactive or inotropic agents, intestinal perforation, diarrhea or ileus, abdominal surgery, total parenteral nutrition and renal replacement therapy (9-12). The presence of bacteremia and previous antibacterial treatment are important risk factors for fungal invasive infections (13,14). It has been reported in a study that half of the patients had positive bacterial blood cultures before the first episode of fungemia and 93% of them used broad-spectrum antibacterial drugs (13). Zhang et al. have also reported that all 55 patients with *Candida* growth in blood culture had a history of prior broad-spectrum antibiotic use, 44 patients used more than three antibiotics, and 37 patients had a history of antibacterial drug use for seven days or more (14). When we evaluated the risk factors in our patients, all patients had received or were receiving antibiotic treatment, the median duration of antibiotic use was seven days (min-max= 1-38 days) and the most commonly used antibiotics were glycopeptides, beta-lactam/beta-lactamase inhibitors and carbapenems. In terms of other risk factors, 26.3% of our patients had a central catheter, 26.3% used TPN, and 27.3% had more than 50% burn area. Only one of our patients had neutropenia and there were no patients with inhalation burns.

In previous studies, it has been observed that candidemia cases occurred most frequently in the 2nd and 3rd weeks after burns (15-17). When the period the growth was detected in our patients was evaluated, it was on the median 13th day of hospitalization and was around the second week, similar to other studies. Devrim et al. found that fungal infections constituted 11.5% of all burn infections in the pediatric burn unit between 2008 and 2015 and the median detection period was similarly 13 days (18). When *Candida* species were compared, *C. albicans* growth was found to be the most common in our study and *C. tropicalis* growth was the second most common. Similarly, in many studies, while *C. albicans* is the most frequently detected fungal species, it is also known that the rate of non-*albicans* species increases (11,17,19). In a study involving pediatric and adult patients with a high rate of *Candida tropicalis, Candida tropicalis* was found to be the most frequently grown *Candida* species in 66.6% of 15 patients with *Candida* growth in blood culture followed up in the burn intensive care unit, and in another study, *Candida tropicalis* was found to be the most frequently grown *Candida* species with a rate of 38% in 27 blood culture samples of 13 patients with *Candida* growth in blood culture (20,21).

Table 4. Evaluation of growths according to the day of hospitalization

***Candida* species that grew**	**Day of hospitalization**				
Day of growth	0-7 days	8-14 days	15-21 days	22-40 days	41-55 days
Candida albicans	4 (19%)	7 (33.4%)	4 (19%)	5 (23.8%)	1 (4.8%)
Non-albicans Candida	4 (23.5%)	5 (29.5%)	4 (23.5%)	3 (17.6%)	1 (5.9%)
Total	8	12	8	8	2

When *Candida albicans* and non-*albicans* growths were compared, no significant difference was found between the two groups in terms of age, sex, serum leukocyte count, neutrophil count, hemoglobin level, platelet count, CRP values and time of growth. Among the two studies conducted in Türkiye comparing patients with *Candida* growth; in the study of Özenen et al. in which *albicans* and non-*albicans* growths were compared, no difference was found between age, sex and laboratory values, while non-*albicans* species were found to be significantly higher in terms of hospitalization time before positive culture and mortality (22). In the study by Çiftdoğan et al. comparing *C. parapsilosis* and non-*parapsilosis Candida* growths, median age, median hospitalization and length of stay in the pediatric intensive care unit have been found to be higher in the parapsilosis group compared to the non-*parapsilosis* group (23).

The limitations of the study are the retrospective collection of case data and the relatively small sample size. In addition, multinominal logistic regression analysis of risk factors between *C. albicans* and non-*albicans Candida* could not be applied due to the limited number of cases. Antifungal susceptibility results could be studied when antifungal kits were available. However, it should be kept in mind that it is limited to *Candida*-associated bloodstream tract infections in pediatric burns.

In conclusion, it is important to keep in mind that infections that develop in pediatric burn patients, especially in the 2nd week (median= 13th day), may be fungal infections, to limit the use of empirical broad-spectrum antimicrobial treatment considering the increase in non-*albicans Candida* species and antifungal drug resistance, and to apply empirical broad-spectrum antimicrobial treatment considering rational antibiotic use.

Ethics Committe Approval: This study approval was obtained from S.B.U. İzmir Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (Decision no: 48, Date: 23.02.2023).

Informed Consent: Patient consent was obtained.

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